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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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Rockville, Maryland 20852

RE: Docket No. 00D-1407
Draft Guidance: ICH S7, Safety Pharmacology Studies for Human Pharmaceuticals

Merck & Co., Inc, is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds or potential drug candidates at the same time through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

Since the inception of the International Conference on Harmonization (ICH), Merck has participated with health authorities from around the globe in the harmonization of regulatory standards. The objectives of ICH are to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical products caused by incompatible regulatory schemes. We continue to monitor the equitable and consistent application of these harmonized standards to product development in order to ensure that new therapies reach patients as swiftly as possible.

In the course of bringing Merck product candidates through developmental testing and clinical trials, Merck scientists regularly address issues affected by this proposed Guidance. Indeed, we have extensive experience in conducting safety pharmacology studies for new molecular entities intended for human use. In addition, Merck commented on early drafts of this Guidance at the request of the ICH Safety Expert Working Group. For these reasons, we are very interested and well qualified to comment on this ICH proposed Guidance.

We commend the Food and Drug Administration for seeking scientifically based harmonized technical procedures for pharmaceutical development through the ICH process. We have reviewed the document in detail and offer the comments below for consideration as this Guidance evolves.

2.3.3 Experimental Design
2.3.3.2 Route of Administration
Lines 131-132, "Regardless of the route of administration, exposure to the parent substance and its major metabolites should be at least similar to or greater than that achieved in humans when such information is available."

Merck comment: A lack of definition could lead to confusion between sponsors and the FDA as to what qualifies as a major metabolite and which metabolites merit evaluation. Therefore, reference to "major metabolites" should be deleted.

2.4 Dose Levels or Concentrations of Test Substances
2.4.1 *In Vivo* Studies
Lines 146-148, "In the absence of adverse effects on safety pharmacology parameters, the highest tested dose should equal or exceed those doses producing some adverse effects in studies of similar route and duration."

Merck comment: Safety pharmacology studies will employ doses several multiples above those necessary for therapeutic effect in humans. When no adverse effects are observed in these safety pharmacology studies, the most appropriate "studies of similar route and administration" to guide selection of the "highest dose" in safety pharmacology studies are multiple dose toxicology studies in the same species. If there are no significant findings in a multiple dose toxicology study, the maximum dose evaluated in subacute toxicity studies should be acceptable as the highest dose for the safety pharmacology studies. The rationale for this proposal is that the safety margin for phase I human dosing is set by the exposure in the multiple dose toxicology study. Exploring larger doses in safety pharmacology studies adds no additional value. Therefore, Merck recommends that Section 2.4.1 be revised to read:

"Safety pharmacology studies should be designed to define the dose response curve of the adverse effects, when they are observed. The time course (e.g. onset and duration of response) of the effects should be investigated when feasible. Generally, the dose response for the adverse effects should be compared to doses necessary for the primary pharmacodynamic response in the test species or the proposed therapeutic effect in humans, if feasible. It is recognized that there are species differences in pharmacodynamic sensitivity. Therefore, doses should include and exceed the primary pharmacodynamic or therapeutic range.

In the absence of adverse effects on safety pharmacology parameters, the highest tested dose should equal or exceed doses producing some adverse effects in studies of similar route and duration, or in the absence of significant toxicological activity, the maximum dose evaluated in the subacute toxicity studies in the same species."

2.6 Studies on Metabolites, Isomers and Finished Products
Lines 176-177, "In vitro or in vivo testing of the individual isomers should also be considered when the product contains the mixture."

Merck recommends testing individual isomers only when tests of the mixture reveal an adverse effect that requires further investigation. The above sentence should be modified to read:

"*In vitro* or *in vivo* testing of the individual isomers should only be considered when tests of the mixture reveal an adverse effect that requires further investigation."

2.6 Studies on Metabolites, Isomers and Finished Products
Lines 178-182, "Safety pharmacology studies with finished product formulation(s) are only necessary for formulations that substantially alter the pharmacokinetics and/or pharmacodynamics of the active substance in comparison to those previously tested (i.e. through active excipients such as penetration enhancers, liposomes, and other changes such as polymorphism)."

Merck comment: Studies with finished product formulation(s) are only necessary for new formulations that substantially increase the pharmacokinetics and/or pharmacodynamics of the active substance in comparison to those previously tested. Therefore, the text above should be modified to read:

"Safety pharmacology studies with finished product formulation(s) are only necessary for formulations that substantially increase the pharmacokinetics and/or pharmacodynamics of the active substance in comparison to those previously tested (i.e. through active excipients such as penetration enhancers, liposomes, and other changes such as polymorphism). A new formulation that substantially decreases exposure to product does not require retesting."

2.9 Conditions Under Which Studies Are Not Necessary
Lines 265-267, "Safety pharmacology core battery studies may be reduced or eliminated for biotechnology-derived products that achieve highly specific receptor targeting."

Merck comment: The core battery studies may be reduced or eliminated for all products that achieve highly specific receptor targeting, including small molecules and biotechnology products. The determination of what products do not require safety pharmacology core battery studies should be based on the degree of receptor targeting, not the type of product. Therefore, the sentence above should read:

"Safety pharmacology core battery studies may be reduced or eliminated for products that achieve highly specific receptor targeting."

2.11 Application Of Good Laboratory Practices
Line 303, "The safety pharmacology core battery is normally conducted under GLP."
Lines 310-311, "Safety pharmacology studies conducted as general screens in the absence of specific cause for concern do not need to be conducted according to GLP."

Merck comment: These two statements appear contradictory. In most cases, a development candidate will be profiled in safety pharmacology studies in a screening mode, which will include vital organs, to identify and characterize unexpected ancillary pharmacological activity. According to Line 310, safety pharmacology studies conducted as general screens need not be conducted according to GLP. Yet Line 303 states the safety pharmacology core battery of vital functions is normally conducted under GLP. The Guidance should clearly state that the core battery is conducted according to GLP and noncore tests may be performed outside of GLP.

In conclusion, the clarification of these points will remove ambiguities concerning the conduct of safety pharmacology studies thereby enabling sponsors to consistently conduct scientifically meaningful studies.

We welcome the opportunity to comment on this Guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,

Dennis M. Erb for,
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Vice President, Regulatory Affairs